Remarks

Currently Claims 1-21, 23, 25-30, 43-44 and 46 are pending. Claims 14 and 16 are amended herein to correct obvious clerical errors. Entry of the foregoing amendment is respectfully requested.

Restriction Requirement and Objection of Claims 1-21, 23 and 43

Applicants acknowledge the Examiner's acceptance of the modified restriction requirement and the election of the claims of Group I for prosecution on the merits at this time. Applicants further acknowledge the withdrawal of claims 25-30, as drawn to a non-elected invention. Claims 25-30 will be cancelled or rejoined upon an indication of allowability of the elected claims.

Applicants respectfully traverse the objection of claims 1-21, 23 and 43 as containing non-elected subject matter. The foregoing claims were properly amended in the response to the restriction requirement to remove the invention of Group II, i.e., compounds of formula (I) wherein two adjacent Q^2 groups together with the carbon atoms to which they are bound, do form a further ring fused to the benzimidazole. In view of this amendment, Applicants respectfully request that the Examiner withdraw the objection of claims 1-21, 23 and 43 or alternatively, specifically indicate by claim and line number the alleged non-elected subject matter in these claims.

Section 112, First Paragraph Rejections Overcome

I. Written Description

Claims 1-19, 21, 23 and 43 currently stand rejected under 35 U.S.C. §112, first paragraph, the Office Action stating that the claims fail to comply with the written description requirement. Applicants respectfully traverse this rejection.

To satisfy the written description requirement under 35 U.S.C. §112, first paragraph, the applicant must describe the invention with reasonable clarity to those of skill in the art as of the filing date sought, convey that he/she was in possession of the invention and that the invention, in that context, is what is now claimed. MPEP 2163.02 (emphasis added). "There is a strong presumption that an adequate written description of the claimed invention is present when the application is filed." MPEP 2163(I)(A). The Examiner has the initial burden, after thorough consideration of the entire specification of presenting evidence or reasons why a person skilled in the art

would not recognize that the written description of the invention provides support for the claims. MPEP 2163(II)(A).

"The written description requirement must be applied in the context of the particular invention and the state of the knowledge [in the art]." *Capon v. Eshhar*, 76 USPQ2d 1078, 1084 (Fed. Cir. 2005). Necessarily the description required to meet written description will vary with the nature and scope of the invention claimed and with the scientific and technological knowledge in the art. *Id.* The analysis requires the examiner to compare the scope of the claims to the scope of the description from the perspective of one skilled in the art. MPEP 2163 (II)(A)(2) pg 2100-178. The Examiner's analysis:

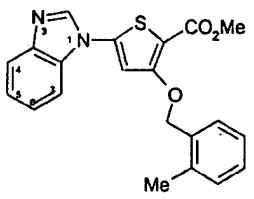
> "should include a determination of the field of the invention and the level of skill and knowledge in the art. Generally, there is an inverse correlation between the level of skill and knowledge in the art and the specificity of the disclosure necessary to satisfy written description." *Id.*

Applicants respectfully submit that the outstanding rejection improperly fails to account for the level of skill in the art at the time of filing. The rejection fails to establish a *prima facie* case for lack of written description because it neither includes a determination of the level of skill in the art nor applies the level of skill in the art in the analysis. Nowhere in paragraph 6 of the office action does the analysis include a description of the level of skill in the art or recognition that the level of skill is relevant to the written description analysis. In paragraph 7, however, the Examiner acknowledges that the level of skill is high, but the rejection fails to apply this high level of skill to the analysis. Accordingly, the Examiner's burden has not been met and the rejection should be withdrawn on these grounds.

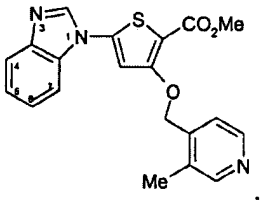
Applicants agree that the level of skill in the art is high and for this reason, a generic formula is normally adequate in chemical cases to meet written description for the claimed genus, because one skilled in the art can visualize many of the species that the claims encompass. *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997) (distinguishing claims to genetic material by name from claims to compounds defined by a generic structural formula). Thus, in the instant case, all that is required is that one skilled in the art be able to "visualize" many of the species encompassed by the generic formula. The Office Action fails to provide any explanation of why one skilled in the art would be unable, based upon the entire

disclosure, to visualize the structures of compounds within the claimed genus wherein Ring A is defined as a other than pyrrolidine, imidazoline, thiophene, furan, cyclohexyl, piperazine, piperidine, tetrahydropyran, morpholine, benzodioxolane and/or wherein R^6 is a substituent that contains a ring other than phenyl. Clearly, one of ordinary skill in the art would be able to visualize the structures of compounds within the full scope of the genus, based upon 1) the structural formula (I), 2) the definitions of variables, including Ring A, and terms, 3) the guidance and direction regarding particular embodiments, and 4) the specific examples. Why would one skilled in the art be unable to identify a species of the inventive compound wherein, for example, Q^1 is defined as formula (ii) wherein Ring A is pyridyl? An example of such structure can readily be drawn by substituting pyridyl for the phenyl ring in the structure of any of numerous exemplified compounds, such as for example, the compound of Example 3:

Example 3



Ring A as pyridyl

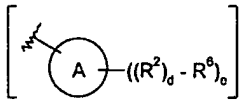


Ring A in claim 1 is defined as selected from the group consisting of ... and 5-10 membered heteroaryl having 1, 2 or 3 heteroatoms selected from N, O and S. "Heteroaryl" is defined at page 12 of the specification as:

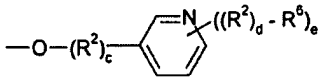
> "The term 'heteroaryl' refers to aromatic monocyclic groups and fused bicyclic groups wherein at least one ring is aromatic, having the specified number of members and containing 1, 2, 3, or 4 heteroatoms selected from N, O and S (unless a different number of heteroatoms is specified). Examples of particular heteroaryl groups include but are not limited to furan, thiophene, pyrrole, imidazole, pyrazole, triazole, tetrazole, thiazole, oxazole, isoxazole, oxadiazole, thiadiazole, isothiazole, pyridine, pyridazine, pyrazine, pyrimidine, quinoline, isoquinoline, benzofuran, benzothiophene, indole, and indazole." Pg 12, lines 1-8.

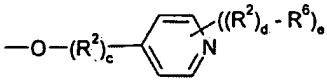
At page 17, lines 22-30 of the specification, Applicants have expressly stated that:

> In one embodiment, Q^1 is defined wherein R^3 is a group of formula (ii)

 and Ring A is selected from the group consisting of ...pyridyl.... In one particular embodiment Ring A is pyridyl. (emphasis added).

Further, at page 18, lines 20-24, state:

"In one particular embodiment, Q^1 is  .

In one particular embodiment, Q^1 is  ."

In both of these sub-structures, the pyridyl ring represents Ring A of Q^1. Thus, there is abundant direction and guidance to one skilled in the art, to the extent of providing sub-structures of Q^1 which clearly depict compounds of formula (I) wherein Q^1 includes a pyridyl ring.

Similar teaching exists for other embodiments of Q^1 and Q^2 as claimed. It is inconceivable based upon the entire description that one skilled in the art would not be able to visualize or recognize the identity of the members of the claimed genus. This is all that is required to meet the standard for written description under section 112. *University of California v. Eli Lilly, supra*. Accordingly, the rejection should be withdrawn.

The Examiner's analysis improperly reasons that structural definition for a chemical compound is insufficient and that either reduction to practice of all species or a correlation between activity and structural elements of Q^1 and Q^2 is required to meet written description. This position is contrary to the law and the MPEP.

> "A specification may ... contain a written description of a broadly claimed invention without describing all species encompassed by the claim. ... In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus." *University of California v. Eli Lilly, supra* at 1406.

Written description for a chemical genus may be satisfied through 1) sufficient description of a representative number of species by actual reduction to practice, 2) reduction to drawing, **or** by disclosure of relevant identifying characteristics, e.g., structure or other physical and/or chemical properties, 3) by functional characteristics coupled with a known or disclosed correlation between function and structure, **or** 4) by a combination of such identifying characteristics. *Id.* at 1406. and MPEP 2163(II)(A)(3)(a)(ii), pg 2100-182. The Examiner is requested to note the use of the conjunction "or" rather than "and" in the passage.

In chemical cases, including the instant claims, a generic structural definition is sufficient to meet the written description guidelines. None of the cases cited by the Examiner establish or suggest otherwise. Based upon the specific structural formula and the definitions provided for variables and terms, one skilled in the art would be able to distinguish compounds of the invention from other compounds and identify many of the species that the claims encompass. Accordingly, the structural formula provided is, without more, sufficient to meet the written description requirement and the rejection should be withdrawn on this basis.

The Examiner's implication that exemplification of virtually all species and/or a specific correlation between activity and structural elements of Q^1 and Q^2 is incorrect. Applicants have not claimed the instant compounds by function, and as such a correlation between structure and function is not required. Applicants have found no case law to support the Examiner's contention that written description for a compound claim reciting a structural formula also requires Applicants to disclose specific elements (pertaining to Q^1 and Q^2) essential for activity. The lack of citation to either the MPEP or case law indicates an improper and legally unsupported analysis, and as such it fails to meet the Examiner's initial burden for providing reasons why one skilled in the art would not have recognized that Applicant was in possession of the inventive compounds described by the structural formula provided. The instant claims do not recite a biomolecule sequence described only by function; --it is those types of non-structural claims that may require a known or disclosed correlation between structure and function (MPEP 2163(I)(A) pg 2100-174). The Cheung article referenced by the Examiner was published approximately 5 years after the filing date of the instant application and thus has no bearing on the analysis because written description must be analyzed as of the filing date of the application.

The Examiner must look at the entire application in analyzing written description, not only the species exemplified. MPEP 2163(II)(A(2) pg 2100-177. Applicants have described 1) a structural formula, 2) definitions of variables and terms employed therein, 3) guidance and direction toward particular embodiments, and 4) a representative number of species –over 150– within the claimed genus. Applicants respectfully submit that *Fujikawa* does not grant the Examiner permission to disregard the definitions of variables and terms and the guidance and direction toward particular embodiments. The selected passage of Fujikawa has been improperly lifted out of context as an attempt to justify complete disregard for a substantial amount of disclosure.

The court in *Fujikawa* denied a count directed toward a selection invention where the application did not include a disclosure of the specific subgenus because the application did not include either *ipsis verbis* support for the selection invention or "blazemarks" in the form of direction toward particular embodiments or preferred embodiments, that lead toward the selection invention. 39 USPQ2d 1895, 1905 (Fed. Cir. 1996). The case in no way supports the Examiner's argument that general teachings of specific listed embodiments do not constitute disclosure for purposes of written description.

In the instant case, the Examiner has rejected the genus and subgenus which <u>are</u> specifically recited in the application. The instant application does contain *ipsis verbis* support and/or blazemarks for the subject matter claimed. *Fujikawa* does not hold that a list of the groups defining a variable is insufficient to support a claim reciting that <u>very same</u> list of groups. This is not and cannot be the law because such a standard would be tantamount to requiring reduction to practice of every single species within the genus. "Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces." MPEP 2163(II)(A)(3)(a)(ii), pg 2100-183.

"What constitutes a 'representative number' [of species to support a genus] is an inverse function of the skill and knowledge in the art." MPEP 2163(II)(A)(3)(a)(ii), pg 2100-183. The Examiner's reliance on *In re Gostelli* as support for the argument that Applicants disclosed species are insufficient to adequately describe the genus, is

misplaced. The court in *Gostelli*, reviewed the Board's decision denying Gostelli the benefit of his prior application, on the "clearly erroneous" standard and found that on the facts of that case, the PTO met their burden by pointing out a number of differences between what was disclosed in the prior application and what Gostelli attempted to claim and on this basis the Board's findings were not *clearly erroneous*. The court did not issue a *per se* rule of what does and does not constitute a representative number of species.

Unlike *Gostelli*, Applicants have provided a structural formula, definitions of variables and term, guidance and direction toward particular embodiments and over 150 individual species. Based on the entirety of Applicants' disclosure, one skilled in the art would clearly recognize that Applicants were in possession of the claimed invention. Accordingly, the instant application meets the written description requirement of section 112, first paragraph and withdrawal of this rejection is respectfully requested.

II. Enablement

Claims 1-19, 21, 23 and 43 currently stand rejected under 35 U.S.C. §112, first paragraph, the Office Action stating that the specification fails to enable those compounds identified in the prior rejection as lacking adequate written description. Applicants respectfully traverse this rejection.

That an element of a claim lacks written description does not necessarily lead to the conclusion that it is also not enabled. MPEP 2164. The test for enablement under 35 U.S.C. §112, first paragraph, is whether the disclosure contains sufficient information to enable one skilled in the pertinent art to make and use the claimed invention without undue experimentation. MPEP 2164.01. The Examiner bears the initial burden of establishing a reasonable basis to question enablement, i.e., why one skilled in the art would doubt the objective truth of the assertions made in the specification with respect to enablement. MPEP 2164.04

The rejection does not state that the specification fails to teach how to make the claimed compounds and the rationale for the rejection is limited to failure to teach how to use the claimed compounds. Accordingly, the Examiner has implicitly acknowledged that the application enables one skilled in the art how to make the

claimed compounds and accordingly, the following remarks address only the "how to use" aspect of the enablement test. If the Examiner intended to reject the claims for failure to teach how to make the claimed compounds, the rejection is so unclear as to preclude response.

The Examiner has recited the relevant factors from *In re Wands* for evaluating undue experimentation, but the rejection does not properly applied those factors to the instant specification or provide the necessary objective evidence to establish a reasonable basis why one skilled in the art would doubt the asserted utility of the claimed compounds.

In the present case, the claims are directed to compounds having a defined structural formula that is (as explained above) fully described by the specification. The claim scope sought finds full support in the written description of the specification, which includes the description of the genus and sub-genuses claimed, definitions of variables and terms, guidance and direction toward particular embodiments for each variable including specific examples of groups defining the same, over 150 exemplified compounds and both enzyme and cellular proliferation data demonstrating inhibition of PLK and cell proliferation for the majority of exemplified compounds. It is well settled that even in unpredictable arts, applicants are not required to disclose every species encompassed by the generic claim in order to satisfy enablement. *Enzo Biochem v. Calgene*, 52 USPQ2d 1129, 188 F3d 1362, 1374 (Fed. Cir. 1999). Accordingly, the scope of the claims is commensurate with the scope of the description.

The relevant art is organic chemistry, including medicinal organic chemistry and Applicants agree with the Examiner that the level of ordinary skill in the art is high.

Applicants respectfully disagree with the Examiner's conclusion that the level of predictability in this case is low because it is not known what structural limitations are required for preservation of activity within the genus. Applicants have provided in the specification both enzyme inhibition and cellular proliferation data for many compounds. The exemplified compounds include a variety of substituents at the positions denoted Q^1 and Q^2. Based upon the variety of the exemplified compounds represented and the biological data provided there is no reason one skilled in the art

would doubt the objective truth of Applicants' asserted utility and the Examiner has not provided objective evidence to establish the contrary. The Cheung publication does not provide the requisite evidence because the publication occurred in July 2007, nearly 5 years after the application priority date. The Examiner is required to consider enablement at the time the invention was made, not in light of publications made 5 years later. Even assuming *arguendo* that the publication were relevant, it pertains not to whether compounds possess *any* activity, but rather to the selection of particular substituents for *optimizing* the properties of a compound for further development. A compound is not "inactive" merely because it does not possess *optimal* properties for further development or because it possess less activity than others in the genus.

The Examiner has argued that without correlation between activity and specific structural elements of Q^1 and Q^2, one skilled in the art would be unable to "predict" what structural modifications within other compounds, would lead to active compounds. This is not the standard for enablement . There is no requirement that one skilled in the art be able to "predict" activity for any compound, be it specifically exemplified or not. All that is required is that one skilled in the art be able to use the invention, based upon the direction and guidance in the application and the knowledge in the art, without undue experimentation.

In ruling on a substantially similar argument, the Court of Appeals for the Federal Circuit overturned the BPAI in *Capon v. Eshhur*, 76 USPQ2d 1078 (Fed. Cir. 2005). In that case, the Board had argued that because success was not assured in the claimed biochemical processes (chimeric DNA encoding single-chain chimeric proteins for expression on the surface of cells of the immune system), the applications lacked sufficient written description and were merely and "invitation to experiment." The Court ruled that the Board had not properly applied the law, holding that generic inventions are not invalid simply because success is not assured. *Id.* at 1086. The court distinguished between generic inventions that are adequately supported and those that are merely a "wish" or "plan" as in *Fiers v. Revel*. The Board grounded its argument in written description, but the court noted that the argument really concerned enablement more than written description, and although the criteria are different, enablement and written description are often met by the same disclosure. *Id.* at 1086-1087.

In the instant case, one skilled in the art be able to ascertain the activity of a compound within the genus without undue experimentation, because screening assays including those specifically described in Applicants' specification, were conventional in the art and required no more than routine experimentation. Even complex experimentation is not undue if the art typically engages in such experimentation. MPEP 2164.01 and *In re Wands, supra*.

In re Wands, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988), is on point with the facts of the instant case. In *Wands*, the claims were to immunoassay methods using a generic class of antibodies. A single hybridoma secreting a single antibody was deposited. The court reversed the examiner's enablement rejection because the application included considerable guidance and direction, the level of skill in the art was high, and all of the methods needed to practice the invention were known in the art, such that those skilled in the art could produce and screen hybridomas secreting other monoclonal antibodies without undue experimentation. Even though not all hybridoma fusions would be successful, the specification was nevertheless enabling. The court determined that "enablement is not precluded by the necessity for some experimentation such as routine screening.... The key word is 'undue,' not 'experimentation'." *Wands* at 736-737.

The art at the time of filing, included the knowledge that enzyme and cellular proliferation assays could be used to evaluate the activity of a given compound for particular kinases, including PLK. Contrary to the Examiner's assertion that the application contains no working examples, Applicants have given both general guidance and specific direction for evaluating activity of any compound within the genus through the use of enzyme and/or cellular proliferation assays. Screening compounds in such assays to determine pharmacological activity is typical and routine experimentation in the art. There were, at the time of filing, known methods for conducting such screening using automated high-throughput screening capable of quickly evaluating activity of thousands of compounds against a plethora of different targets. Methods for conducting such screens are also provided in the Applicants' specification at pages 195-197. Inasmuch as this experimentation is routine in the art and described in the specification, it does not constitute undue experimentation pursuant to *In re Wands*.

The Examiner is also reminded that "[i]t is not necessary for every permutation within a generally operable invention to be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention. *Capon v. Eshhar, supra* at 1087. The presence of inoperative embodiments within the scope of a claim does not necessarily render the claim nonenabled. MPEP 2164.08(b). The standard is whether a person of ordinary skill could determine which embodiments would be inoperative with expenditure of no more effort than is normally required in the art. *Id.* The evaluation of activity of embodiments within the genus may be conducted using routine experimentation in the art. Accordingly it is respectfully submitted that the pending claims are fully enabled by the specification and withdrawal of this rejection is therefore respectfully requested.

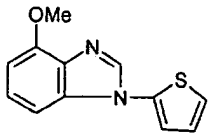
Section 112, Second Paragraph Rejection Overcome

The foregoing amendment to claim 16, correcting the inadvertent clerical error by changing "and" to "or," overcomes the outstanding rejection of that claim under 35 U.S.C. §112, second paragraph. Withdrawal of the rejection is respectfully requested.

Section 102(b) Rejections Overcome

Claims 1, 15-19 and 21 currently stand rejected under 35 U.S.C. §102(b), the Office Action stating that they are anticipated by Palmer et al., *J. Med. Chem.* 1998 **41**:5457-5465 (Palmer). Applicants respectfully traverse this rejection.

The Office Action states that Palmer teaches a compound of formula



which the Examiner asserts corresponds to Applications formula (I) wherein *inter alia* $Q^1 = -(R^2)_a-(Y^1)_b-(R^2)_c-R^3$ where a=b=c=0 and R^3=H.

Applicants respectfully submit that the Examiner has not considered the entire claim. Claim 1 recites a compound of formula (I) wherein "a, b and c are the same or

different and are each independently 0 or 1 and at least one of a or b is 1." See claim 1, lines 21-22 above.

Hence, according to Applicants' claims, the thiophenyl ring must be substituted at the position denoted by Q^1. Palmer neither discloses nor suggests the instantly claimed compounds having a thiophenyl substituent at this position. Accordingly, Palmer fails to teach or suggest all of the elements of claim 1, and by extension dependent claims 15-19 and 21, and therefore does not anticipate the instantly pending claims. Withdrawal of the instant rejection and examination of the remaining species in the genus is respectfully requested.

Supplemental IDS

Applicants have filed concurrently herewith a supplemental information disclosure statement and PTO-1449. Consideration of the documents cited thereon and return of an initialed copy of the PTO-1449 with the next communication is respectfully requested.

Applicants respectfully submit that the instant application is in condition for allowance, which action is respectfully requested. The Examiner is invited to contact the undersigned at (919) 483-8222, to discuss this case, if desired.

Respectfully submitted,

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Attorney for Applicants
Registration No. 38,181

Date: 30 Nov 2007

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